CLAIMS

1. A nucleic acid vector comprising:
   (a) a nucleic acid sequence encoding a human Tau protein;
   (b) a sequence capable of directing expression of said human Tau protein in the nervous system of a non-human animal; and
   (c) a targeting sequence which facilitates integration of said vector into the genome of said animal so as to prevent expression of equivalent Tau protein or a related or equivalent protein from said animal in favour of said human Tau protein.

2. A vector according to claim 1 further comprising a sequence encoding a reporter molecule.

3. A vector according to claim 2 wherein said reporter molecule comprises the hygromycin Pgk-hyg marker gene sequence.

4. A vector according to any of claims 1 to 3 wherein said sequence encoding human Tau is a cDNA sequence.

5. A vector according to claim 4 wherein said cDNA sequence encodes a Tau 40 isoform.

6. A vector according to any preceding claim wherein said sequence capable of directing expression of said human Tau protein is a mouse promoter.

7. A vector according to claim 6 wherein said mouse promoter is a Thy-1 promoter.

8. A vector according to claim 7 wherein said targeting sequence comprises a nucleotide sequence exhibiting a sufficient degree of homology with said sequence encoding said equivalent Tau protein in said animal or flanking sequences thereof, to facilitate integration of said vector into the genome of said animal by homologous recombination.

9. A vector according to claim 8 wherein said targeting sequence comprises a NcoI restriction site corresponding to the unique NcoI restriction site of exon1 of the mouse wild type genome.

10. A vector according to any of claims 1 to 9 further comprising two loxP sites flanking either of the sequences of step (a) and (b).

11. A vector according to any of claims 1 to 9 further comprising a stop sequence capable of preventing expression of said human Tau protein and which sequence is flanked by two loxP sites capable of undergoing reciprocal conservative DNA recombination in the presence of Cre recombinase with the resulting excision of said stop sequence.

12. A nucleic acid vector comprising:

(a) a nucleic acid sequence encoding a human protein capable of modulating human Tau protein;

(b) a sequence capable of directing expression of said protein in the nervous system of said animal; and

(c) a targeting sequence capable of facilitating integration of said vector into the genome

of said animal optionally at a position corresponding to a sequence in said animal encoding an equivalent of said human protein so as to prevent expression of said equivalent sequence in favour of said human protein capable of modulating human Tau protein.

13. A vector according to claim 12 wherein said human protein is capable of phosphorylating a human Tau protein.

14. A vector according to claim 12 or 13 wherein said human protein is GSK-3β kinase.

15. A vector according to any of claims 12 to 14 wherein said nucleic acid sequence in step a) is a cDNA sequence.

16. A vector according to any of claims 12 to 15 wherein said sequence capable of directing expression of said protein capable of modulating human Tau protein is a mouse promoter.

17. A vector according to claim 16 wherein said promoter is a Thy-1 promoter.

18. A vector according to any of claims 12 to 16 further comprising two loxP sites flanking either of the sequences of step (a) and (b).

19. A vector according to any of claims 12 to 17 further comprising a stop sequence capable of

preventing expression of said protein capable of modulating human Tau protein, and which stop sequence is flanked by two loxP sites capable of undergoing reciprocal conservative DNA recombination in the presence of Cre recombinase with the resulting excision of the stop sequence.

20. A host cell transformed, transfected or injected with a vector according to any one of the preceding claims.

21. A host cell according to claim 20 wherein the cell is a non-human animal cell.

22. A host cell according to claim 21 wherein said non-human animal cell is a non-human mammalian embryo cell.

23. A host cell according to claim 22 wherein said cell is an embryonic stem cell.

24. A method of making a transgenic non-human animal comprising the steps of:

(a) introducing into an embryo cell of said animal one or more of a nucleic acid vector according to any of claims 1 to 19;

(b) introducing the embryo from step (a) into a female animal;

(c) sustaining the female in step (b) until such time as the embryo has sufficiently developed and is borne from the female; and

(d) sustaining the transgenic animal.

25. A method according to claim 24 wherein said vector is introduced firstly into an embryonic stem

cell which is subsequently introduced into a blastocyst of said animal.

26. A method according to claim 25 wherein both of the vectors encoding said human Tau and said protein capable of modulating human Tau according to claims 1 to 11 and 12 to 19 respectively are introduced into said stem cell.

27. A method according to any of claims 24 to 26 wherein said non-human animal is a mammal.

28. A method according to claim 27 wherein said mammal is a mouse.

29. A method according to claim 24 or 25, comprising the step of introducing a vector according to any of claims 1 to 11 into a first animal and a vector according to any of claims 12 to 19 into a second animal, crossing said first and second animals and selecting among the progeny those that express both said human Tau and said protein capable of modulating human Tau protein.

30. A method of making a transgenic non-human animal, which expresses a human Tau protein comprising the steps of:

(a) introducing sequentially or simultaneously into an embryo cell of said animal a first nucleic acid vector comprising a transgene capable of expressing said human Tau protein in the nervous system of said animal and a second nucleic acid vector comprising a sequence of nucleotides which upon integration into the genome of said animal

is capable of preventing expression of endogenous Tau protein from said animal;

(b) introducing the embryo from step (a) into a female animal,

(c) sustaining the female in step (b) until such time as the embryo has sufficiently developed and is borne from the female; and

(d) sustaining the transgenic animal.

31. A method according to claim 30 wherein each of said first and second nucleic acid vectors are introduced in the same embryo cell.

32. A method according to claim 30 or 31 wherein said transgenic non-human animal is a mammal.

33. A method according to claim 32 wherein said mammal is a mouse.

34. A method according to any of claims 30 to 33 wherein said second nucleic acid vector comprises a sequence of nucleotides comprising a region of homology with a sequence encoding an equivalent Tau protein in said animal or with a region flanking or adjacent said sequence so as to facilitate integration of said vector into the genome of said animal by homologous recombination.

35. A method of generating a transgenic non-human animal which is a model for Alzheimers disease or related neurodegenerative disorders, comprising the steps of crossing a first transgenic non-human animal comprising a vector according to any of claims 1 to 11 in its genome with a second transgenic non-human animal comprising a vector according to any of claims

12 to 19 in its genome selecting among the progeny those that express both human Tau protein and said kinase.

36. A method according to claim 35 wherein said nucleic acid vector in said first transgenic animal comprises a vector according to claim 10 or 11.

37. A method according to claim 36 wherein said second transgenic animal comprises a vector according to any of claims 12 to 19.

38. A method according to claim 34 which further comprises introducing into said second animal a vector comprising a transgene encoding Cre recombinase.

39. A transgenic non-human animal obtainable according to the methods of any of claims 24 to 38.

40. A transgenic non-human animal that is a model for neurodegenerative disorders, comprising:

(a) an introduced DNA sequence encoding and capable of expressing the protein Tau in the nervous system of the animal; and

(b) a DNA sequence encoding and capable of expressing a protein capable directly or indirectly of modulating Tau protein.

41. A transgenic non-human animal according to claim 40 wherein said sequence in step (a) comprises a vector according to any of claims 1 to 11.

42. A transgenic non-human animal according to claim 40 wherein said sequence according to step (b) comprises a vector according to any of claims 12 to 19.

43. A method of identifying a compound which modulates human kinase mediated phosphorylation of human Tau protein which method comprises administering a test compound to a non-human animal according to any of claims 39 to 42 expressing both said human Tau protein and said human kinase and monitoring the phosphorylation profile of said Tau protein compared to one of said transgenic animals which has not been administered with the compound.

44. A compound obtainable according to the method of claim 43.

45. A pharmaceutical composition comprising a compound according to claim 44 together with a pharmaceutically acceptable carrier, diluent or excipient therefor.

46. Use of a compound according to claim 44 in the manufacture of a medicament for the treatment of neurodegenerative disorders.

47. Use according to claim 46, wherein said neurodegenerative disorders comprise any of FTDP-17 (Fronto-temporal dementia associated with Parkinson=s disease), Cortico-basal degeneration, progressive supranuclear palsy, multiple system atrophy , Pick=s disease, Dementia Pugilistica, Dementia with tangles only, dementia with tangles and calcification, Down syndrome, Myotonic dystrophy, Niemann Pick=s disease type C, Parkinsonism-dementia complex of Guam, Postencephalic Parkinsonism, Prion diseases with tangles, subacute sclerosing panencephalitis.

48. A method of treating neurodegenerative disorders mediated by phosphorylation of human Tau protein comprising administering to a patient a compound as defined in claim 44 or a composition according to claim 45.

49. A method of generating a transgenic non-human animal which is a model for Alzheimers disease or related neurodegenerative disorders, comprising the steps of crossing a first transgenic non-human animal comprising a vector having, i) a nucleic acid sequence encoding a human Tau protein, ii) a sequence capable of directing expression of said human Tau protein in the nervous system of said animal and iii) a targeting sequence which facilitates integration of said vector into the genome of said animal, with a second transgenic non-human animal comprising a vector according to claim 12, selecting among the progeny those that express both human Tau protein and said protein capable of modulating Tau protein.

50. A method according to claim 49 wherein said vector in said first and/or said second transgenic non-human animal comprises a stop sequence capable of preventing expression of said human Tau protein or said protein capable of modulating Tau protein which sequence is flanked by two loxP sites capable of undergoing reciprocal conservative DNA recombination with the resulting excision of said stop sequence.

51. A transgenic non-human animal obtainable according to the method of claim 49 or 50.